10553957

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Welcome to STN International! Enter x:x

LOGINID:SSSPTA1626GMS

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 3	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 4	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 5	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 6	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 7	AUG 27	USPATOLD now available on STN
NEWS 8	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 9	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 10	SEP 13	FORIS renamed to SOFIS
NEWS 11	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 12	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 13	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 14	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 15	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 16	OCT 19	BEILSTEIN updated with new compounds
NEWS 17	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 18	NOV 19	WPIX enhanced with XML display format
NEWS 19	NOV 30	ICSD reloaded with enhancements
NEWS 20	DEC 04	LINPADOCDB now available on STN
NEWS 21	DEC 14	BEILSTEIN pricing structure to change
NEWS 22	DEC 17	USPATOLD added to additional database clusters
NEWS 23	DEC 17	IMSDRUGCONF removed from database clusters and STN
NEWS 24	DEC 17	DGENE now includes more than 10 million sequences
NEWS 25	DEC 17	TOXCENTER enhanced with 2008 MeSH vocabulary in MEDLINE segment
NEWS 26	DEC 17	MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
NEWS 27	DEC 17	CA/CAplus enhanced with new custom IPC display formats
NEWS 28	DEC 17	STN Viewer enhanced with full-text patent content from USPATOLD
NEWS 29	JAN 02	STN pricing information for 2008 now available

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),

AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items
NEWS IPC8 For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:56:08 ON 07 JAN 2008

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 13:56:20 ON 07 JAN 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6
DICTIONARY FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

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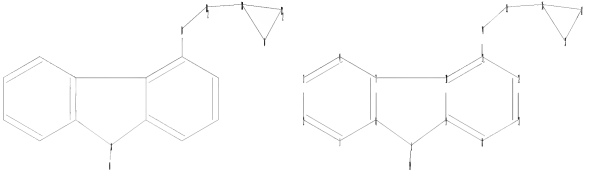
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information

on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\10553957.str

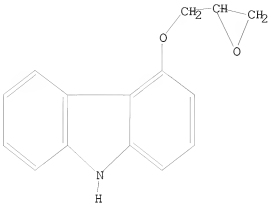


chain nodes :
14 15 19
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18
chain bonds :
5-19 11-14 14-15 15-16
ring bonds :
1-2 1-6 2-3 3-4 4-7 5-6 5-9 6-7 7-10 8-9 8-13 9-10 10-11 11-12 12-13
16-17 16-18 17-18
exact/norm bonds :
5-6 5-9 11-14 16-17 16-18 17-18
exact bonds :
5-19 7-10 14-15 15-16
normalized bonds :
1-2 1-6 2-3 3-4 4-7 6-7 8-9 8-13 9-10 10-11 11-12 12-13
isolated ring systems :
containing 1 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom 19:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

```
=> s l1
SAMPLE SEARCH INITIATED 13:56:34 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        5 TO ITERATE

100.0% PROCESSED         5 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:             5 TO      234
PROJECTED ANSWERS:                0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 13:56:41 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       73 TO ITERATE

100.0% PROCESSED        73 ITERATIONS                                 14 ANSWERS
SEARCH TIME: 00.00.01

L3           14 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     178.36     178.57

FILE 'HCAPLUS' ENTERED AT 13:56:46 ON 07 JAN 2008
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COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 7 Jan 2008 VOL 148 ISS 2
FILE LAST UPDATED: 6 Jan 2008 (20080106/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 48 L3

=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.83	197.40

FILE 'REGISTRY' ENTERED AT 14:01:10 ON 07 JAN 2008
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6
DICTIONARY FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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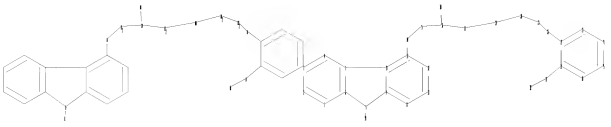
Uploading C:\Program Files\Stnexp\Queries\10553957a.str

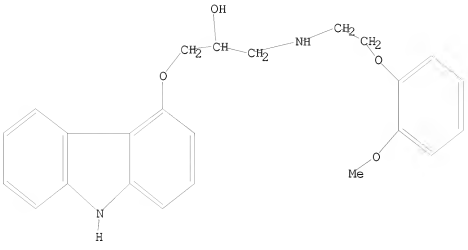


chain nodes :
14 15 16 17 18 26 27 28 29 30 31 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 20 21 22 23 24 25
chain bonds :
5-18 11-14 14-15 15-16 16-17 16-30 17-29 21-31 22-26 26-27 27-28 28-29
31-32
ring bonds :
1-2 1-6 2-3 3-4 4-7 5-6 5-9 6-7 7-10 8-9 8-13 9-10 10-11 11-12 12-13
20-21 20-25 21-22 22-23 23-24 24-25
exact/norm bonds :
5-6 5-9 11-14 16-30 21-31 22-26
exact bonds :
5-18 7-10 14-15 15-16 16-17 17-29 26-27 27-28 28-29 31-32
normalized bonds :
1-2 1-6 2-3 3-4 4-7 6-7 8-9 8-13 9-10 10-11 11-12 12-13 20-21 20-25
21-22 22-23 23-24 24-25
isolated ring systems :
containing 1 : 20 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:CLASS 20:CLASS
21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:CLASS 27:CLASS 28:CLASS
29:CLASS 30:CLASS 31:CLASS 32:CLASS

L5 STRUCTURE UPLOADED

=> d 15
L5 HAS NO ANSWERS
L5 STR



Structure attributes must be viewed using STN Express query preparation.

```
=> s l5
SAMPLE SEARCH INITIATED 14:01:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        8 TO ITERATE

100.0% PROCESSED        8 ITERATIONS                                4 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            8 TO      329
PROJECTED ANSWERS:               4 TO      200

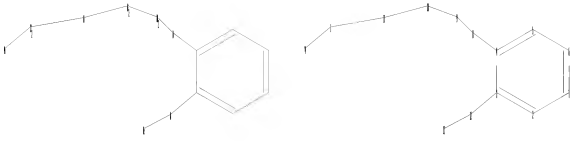
L6             4 SEA SSS SAM L5

=> s l5 sss full
FULL SEARCH INITIATED 14:01:37 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      301 TO ITERATE

100.0% PROCESSED      301 ITERATIONS                               95 ANSWERS
SEARCH TIME: 00.00.01

L7            95 SEA SSS FUL L5

=>
Uploading C:\Program Files\Stnexp\Queries\10553957b.str
```

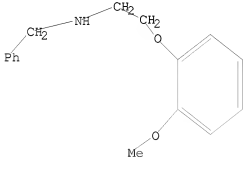


chain nodes :
1 8 9 10 11 12 13 14
ring nodes :
2 3 4 5 6 7
chain bonds :
1-11 1-14 3-12 4-8 8-9 9-10 10-11 12-13
ring bonds :
2-3 2-7 3-4 4-5 5-6 6-7
exact/norm bonds :
3-12 4-8
exact bonds :
1-11 1-14 8-9 9-10 10-11 12-13
normalized bonds :
2-3 2-7 3-4 4-5 5-6 6-7

Match level :
1:Atom 2:CLASS 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS

L8 STRUCTURE UPLOADED

=> d l8
L8 HAS NO ANSWERS
L8 STR



Structure attributes must be viewed using STN Express query preparation.

```
=> s l8
SAMPLE SEARCH INITIATED 14:04:09 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      686 TO ITERATE

100.0% PROCESSED      686 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:         12149 TO    15291
PROJECTED ANSWERS:                1 TO       80

L9            1 SEA SSS SAM L8

=> s l8 sss full
FULL SEARCH INITIATED 14:04:15 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    13036 TO ITERATE

100.0% PROCESSED    13036 ITERATIONS                               15 ANSWERS
SEARCH TIME: 00.00.01

L10           15 SEA SSS FUL L8

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   358.10     555.50

FILE 'HCAPLUS' ENTERED AT 14:04:20 ON 07 JAN 2008
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FILE COVERS 1907 - 7 Jan 2008  VOL 148 ISS 2
FILE LAST UPDATED: 6 Jan 2008  (20080106/ED)

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 substance identification.

=> d his

     (FILE 'HOME' ENTERED AT 13:56:08 ON 07 JAN 2008)
```

```
     FILE 'REGISTRY' ENTERED AT 13:56:20 ON 07 JAN 2008
L1                STRUCTURE UPLOADED
L2             0 S L1
L3            14 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 13:56:46 ON 07 JAN 2008
L4            48 S L3

     FILE 'REGISTRY' ENTERED AT 14:01:10 ON 07 JAN 2008
L5                STRUCTURE UPLOADED
L6             4 S L5
L7            95 S L5 SSS FULL
L8                STRUCTURE UPLOADED
L9             1 S L8
L10           15 S L8 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:04:20 ON 07 JAN 2008

=> s l7
L11       1715 L7

=> s l10
L12         28 L10

=> s l4 and l12
L13          9 L4 AND L12

=> s l13 and catalyst
        786783 CATALYST
        783681 CATALYSTS
       1006285 CATALYST
                  (CATALYST OR CATALYSTS)
L14          3 L13 AND CATALYST

=> s l14 and zncl2
         38620 ZNCL2
L15          1 L14 AND ZNCL2

=> s l11 and process
       2546449 PROCESS
       1733561 PROCESSES
       3795605 PROCESS
                  (PROCESS OR PROCESSES)
L16        116 L11 AND PROCESS

=> s l16 and l4
L17         14 L16 AND L4

=> s l16 and l12
L18          6 L16 AND L12

=> s l17 and catalyst
        786783 CATALYST
        783681 CATALYSTS
       1006285 CATALYST
                  (CATALYST OR CATALYSTS)
L19          2 L17 AND CATALYST
```

```
=> s l18 and catalyst
        786783 CATALYST
        783681 CATALYSTS
       1006285 CATALYST
                 (CATALYST OR CATALYSTS)
L20           2 L18 AND CATALYST

=> d his

     (FILE 'HOME' ENTERED AT 13:56:08 ON 07 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 13:56:20 ON 07 JAN 2008
L1              STRUCTURE UPLOADED
L2            0 S L1
L3           14 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 13:56:46 ON 07 JAN 2008
L4           48 S L3

     FILE 'REGISTRY' ENTERED AT 14:01:10 ON 07 JAN 2008
L5              STRUCTURE UPLOADED
L6            4 S L5
L7           95 S L5 SSS FULL
L8              STRUCTURE UPLOADED
L9            1 S L8
L10          15 S L8 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:04:20 ON 07 JAN 2008
L11        1715 S L7
L12          28 S L10
L13           9 S L4 AND L12
L14           3 S L13 AND CATALYST
L15           1 S L14 AND ZNCL2
L16         116 S L11 AND PROCESS
L17          14 S L16 AND L4
L18           6 S L16 AND L12
L19           2 S L17 AND CATALYST
L20           2 S L18 AND CATALYST

=> d l3 ibib abs hitstr tot
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:end

=> d l13 ibib abs hitstr tot

L13  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2005:1260624  HCAPLUS
DOCUMENT NUMBER:          144:22806
TITLE:                    Process for the preparation of carvedilol
INVENTOR(S):              Kankan, Rajendra Narayanrao; Rao, Dharmaraj
                          Ramachandra
PATENT ASSIGNEE(S):       Cipla Limited, India; Wain, Christopher Paul
SOURCE:                   PCT Int. Appl., 29 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
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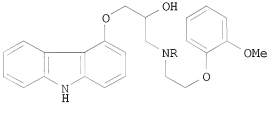
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005113502	A1	20051201	WO 2005-GB1978	20050519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005245182	A1	20051201	AU 2005-245182	20050519
CA 2566197	A1	20051201	CA 2005-2566197	20050519
EP 1756057	A1	20070228	EP 2005-744187	20050519
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2007538061	T	20071227	JP 2007-517424	20050519
IN 2006MN01302	A	20070608	IN 2006-MN1302	20061107
PRIORITY APPLN. INFO.:			GB 2004-11273 A	20040520
			WO 2005-GB1978 W	20050519

OTHER SOURCE(S): CASREACT 144:22806

GI



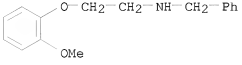
I

AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H4O(CH2)2NHCH2Ph using K2CO3 in water to give carvedilol N-benzyl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pd/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic β-receptor antagonists, vasodilators and treatment of angina pectoris.

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)

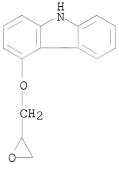
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1128799 HCAPLUS
DOCUMENT NUMBER: 143:386916
TITLE: An improved process for the manufacture of carvedilol
INVENTOR(S): Kankan, Rajendra Narayan Rao; Rao, Dharamraj Ramchandra
PATENT ASSIGNEE(S): Cipla Ltd., India
SOURCE: Indian, 11 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 186587	A1	20011006	IN 1999-BO583	19990817

PRIORITY APPLN. INFO.: IN 1999-BO583 19990817
OTHER SOURCE(S): CASREACT 143:386916; MARPAT 143:386916
GI

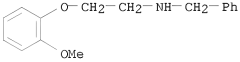
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An improved process for the manufacture of Carvedilol I, a potent antihypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [R1 = (un)substituted CH2Ph; formed by reacting carbazole III with a substituted amine IV]. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl]benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [R1 = Ch2Ph] afforded carvedilol I.

IT 120606-08-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(improved process for the manufacture of carvedilol)

RN 120606-08-8 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

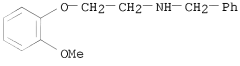


● HCl

IT 3246-03-5 51997-51-4, 4-(2,3-Epoxypropoxy)carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(improved process for the manufacture of carvedilol)

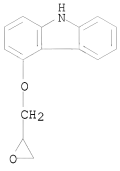
RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L13 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019

PRIORITY APPLN. INFO.:

IN 2003-MU647	A	20030620
IN 2003-MU721	A	20030717
WO 2004-IN52	W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

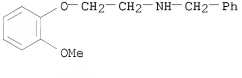
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine
51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1, (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2, (R)-4-(Oxiranylmethoxy)-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

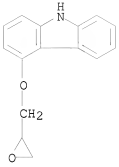
RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



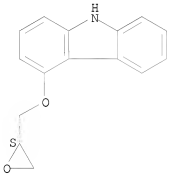
RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



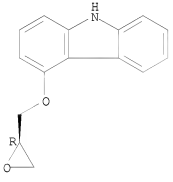
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 2004127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

PRIORITY APPLN. INFO.:

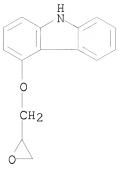
EP 2001-101584	A	20010125
US 2002-54462	A3	20020122
WO 2002-EP583	W	20020122

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

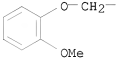
AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.

IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747162 HCAPLUS
DOCUMENT NUMBER: 135:288690
TITLE: Intermediates for preparing the R- or S- enantiomer and N-benzyl derivatives of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001

RU 2216539	C2	20031120	RU 1998-120700		19981118
RU 2245875	C2	20050210	RU 2003-107772		19981118
EP 918055	A1	19990526	EP 1998-122114		19981124
EP 918055	B1	20030423			
EP 918055	B2	20060426			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:	HU 1997-2209	A 19971124
	HU 1998-2180	A 19981001
	EP 1998-122114	A3 19981124
	RU 1998-120700	A 19981118

OTHER SOURCE(S): CASREACT 135:288690

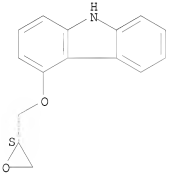
AB R-(+)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol-4'''-yloxy]propan-2-ol and S-(-)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9''H-carbazol-4'''-yloxy]propan-2-ol and the R- or S- enantiomer of carvedilol are prepared in high yield and selectivity by the ring-opening cleavage of the resp. R- or S- enantiomer of 4-(oxiranylmethoxy)-9H-carbazole with N-2-[(2'-methoxyphenoxy)ethyl]benzylamine to give the N-benzyl derivs., and the chiral carvedilol enantiomers are prepared by the reductive debenzylation of the resp. chiral N-benzyl derivs. in the presence of Pd/C and hydrazine hydrate.

IT 95093-95-1, S-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2, R-4-(Oxiranylmethoxy)-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs. of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

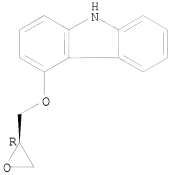
Absolute stereochemistry.



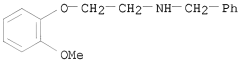
RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

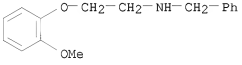
Absolute stereochemistry. Rotation (-).



IT 3246-03-5P 120606-08-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs. of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



RN 120606-08-8 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L13 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747161 HCAPLUS
DOCUMENT NUMBER: 135:288689
TITLE: Process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-ol [carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

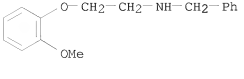
PRIORITY APPLN. INFO.:
HU 1997-2209 A 19971124
HU 1998-2180 A 19981001
EP 1998-122114 A3 19981124
RU 1998-120700 A 19981118

OTHER SOURCE(S): CASREACT 135:288689

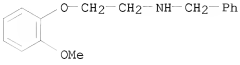
AB A process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol as well as acid addition salts of this compound, was developed in which the N-[2-(2'-methoxy-phenoxy)-ethyl]benzylamine is reacted with epichlorohydrin, and the formed 1-N-benzyl-2'-[{(2'-methoxy-phenoxy)ethyl}amino]-3-propan-2-ol is reacted with 4-hydroxy-9H-carbazole and the resulting 1-N-benzyl-2'-(methoxyphenoxyethylamino)-3-[9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol thus obtained is reacted with acids to yield acid addition their salts, or if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2}-(2'-methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts thereof and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-{2}-(2'-methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, separating the enantiomers.

IT 3246-03-5P 120606-08-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

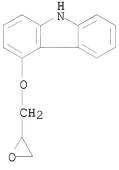
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



RN 120606-08-8 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)



IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L13 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:344783 HCAPLUS
DOCUMENT NUMBER: 130:352184
TITLE: Preparation of carvedilol
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
CZ 296521	B6	20060412	CZ 1998-3561	19981104
CZ 297445	B6	20061213	CZ 2004-1111	19981104
HR 980590	B1	20031231	HR 1998-590	19981112
SK 284109	B6	20040908	SK 1998-1560	19981112
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
ES 2196459	T3	20031216	ES 1998-122114	19981124
ES 2221875	T3	20050116	ES 2001-111213	19981124

PRIORITY APPLN. INFO.:

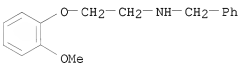
HU 1997-2209	A	19971124
HU 1998-2180	A	19981001
RU 1998-120700	A	19981118
EP 1998-122114	A3	19981124

AB The title process comprises, e.g., condensation of 4-oxiranylmethoxy-9H-carbazole with 2-(MeO)C6H4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.

IT 3246-03-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol)

RN 3246-03-5 HCAPLUS

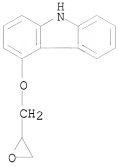
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



IT 51997-51-4, 4-Oxiranylmethoxy-9H-carbazole 95093-95-1, (S)-4-Oxiranylmethoxy-9H-carbazole 95093-96-2, (R)-4-Oxiranylmethoxy-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carvedilol)

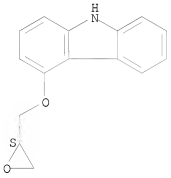
RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



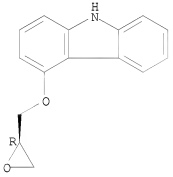
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

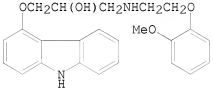
Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

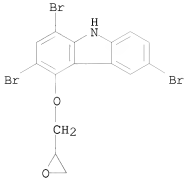
L13 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1994:270010 HCAPLUS
DOCUMENT NUMBER: 120:270010
TITLE: Synthesis of the enantiomers and three racemic metabolites of Carvedilol labeled to high specific activity with tritium
AUTHOR(S): Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.; Garnes, K. T.; Heys, J. R.
CORPORATE SOURCE: Dep. Synth. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1993), 33(12), 1091-105
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

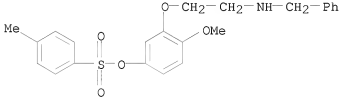


I

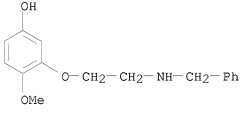
AB Carvedilol (SK&F 105517) (I) possesses unique cardiovascular activity, and is under development for indications such as angina and hypertension. Tritium labeled enantiomers of Carvedilol and racemates of three metabolites were needed for pharmacol. and drug metabolic studies. These compds. were synthesized by catalytic tritium-halogen exchange using tritium gas and 10% palladium-on-carbon catalyst. The precursors were polyhalogenated in the carbazole ring. Direct electrophilic bromination of the enantiomers of Carvedilol gave precursors that were converted to the corresponding tritiated final products by catalytic tritium halogen exchange. Bromination of 4-(2,3-epoxypropyloxy)-9H-carbazole gave an intermediate that was converted to the halogenated precursors of the racemic metabolites. Elaboration of this intermediate, 1,3,6-tribromo-4-(2,3-epoxypropyloxy)-9H-carbazole, to the desired metabolite precursors was achieved by nucleophilic epoxide opening with suitably functionalized N-benzyl aryloxyethylamines. Catalytic tritium-halogen exchange upon the brominated metabolite precursors was accompanied by cleavage of N- and O-benzyl protecting groups. Radiochem. purities of all tritiated final products were greater than 98% after preparative HPLC. Specific activities of the final products, determined by mass spectrometry, ranged from 35 to 76 Ci/mmol. Optical purity of the Carvedilol enantiomers, determined by chiral HPLC, was greater than 99%.
IT 154582-49-7P 154582-52-2P 154582-53-3P
154582-56-6P 154582-57-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate in preparation of tritium labeled Carvedilol)
RN 154582-49-7 HCAPLUS
CN 9H-Carbazole, 1,3,6-tribromo-4-(oxiranylmethoxy)- (9CI) (CA INDEX NAME)



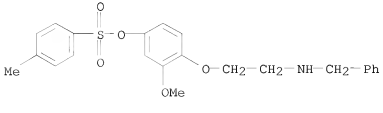
RN 154582-52-2 HCAPLUS
CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)



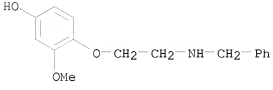
RN 154582-53-3 HCAPLUS
CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)



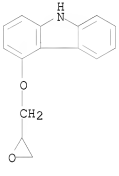
RN 154582-56-6 HCAPLUS
CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)



RN 154582-57-7 HCAPLUS
CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)



IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant, in preparation of tritium labeled Carvedilol)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L13 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1980:128716 HCAPLUS
DOCUMENT NUMBER: 92:128716
ORIGINAL REFERENCE NO.: 92:20983a,20986a
TITLE: Carbazolyl-4-oxypropanolamine derivatives
INVENTOR(S): Wiedemann, Fritz; Kampe, Wolfgang; Thiel, Max; Sponer, Gisbert; Roesch, Egon; Dietmann, Karl
PATENT ASSIGNEE(S): Boehringer Mannheim G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 27 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2815926	A1	19791018	DE 1978-2815926	19780413
CA 1129416	A1	19820810	CA 1979-324667	19790402
DK 7901419	A	19791014	DK 1979-1419	19790406
DK 154555	B	19881128		
DK 154555	C	19890619		

FI 7901142	A	19791014	FI 1979-1142		19790406
FI 70406	B	19860327			
FI 70406	C	19860912			
AU 7945820	A	19791018	AU 1979-45820		19790406
AU 522975	B2	19820708			
ES 479396	A1	19800416	ES 1979-479396		19790406
SU 810079	A3	19810228	SU 1979-2745301		19790406
EP 4920	A1	19791031	EP 1979-101063		19790407
EP 4920	B1	19810805			
R: BE, CH, DE, FR, GB, IT, LU, NL, SE					
IL 57020	A	19820730	IL 1979-57020		19790408
DD 143607	A5	19800903	DD 1979-212096		19790409
CS 227007	B2	19840416	CS 1979-2434		19790410
JP 54157558	A	19791212	JP 1979-43119		19790411
JP 01023462	B	19890502			
ZA 7901732	A	19800528	ZA 1979-1732		19790411
HU 21840	A2	19820227	HU 1979-BO1774		19790412
HU 179433	B	19821028			
AT 7902762	A	19840115	AT 1979-2762		19790412
AT 375639	B	19840827			
CS 227047	B2	19840416	CS 1982-6106		19820820
US 4503067	A	19850305	US 1983-479921		19830404
JP 63258416	A	19881025	JP 1987-76548		19870331
PRIORITY APPLN. INFO.:			DE 1978-2815926	A	19780413
			US 1979-21394	A1	19790316
			CS 1979-2434	A3	19790410
			US 1980-198975	A1	19801021

OTHER SOURCE(S): MARPAT 92:128716
GI

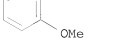
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A wide range of I (R = H, lower alkyl, or aroyl; R1 = H, lower alkyl, or aralkyl, R2 and R3 independently were H or lower alkyl, X = CH2, O, S, or valence bond; Ar = mono- or bicyclic aryl or pyridyl) (.apprx.50 compds.) were prepared as β-sympatholytics and vasodilators (no data), in most cases by reaction of 4-(oxiranylmethoxy)carbazole (II) with an amine. Thus, 6.0 g II and 7.6 g 2-MeOC6H4CH2CH2NH2 were stirred 20 h at 70° to give 61% III. Also prepared were, e.g., IV and V.

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (oxiranylmethoxy)carbazole)

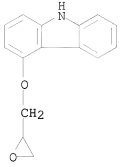
RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, with amines)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



=> d l14 ibib abs hitstr tot

L14 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647 A	20030620
			IN 2003-MU721 A	20030717
			WO 2004-IN52 W	20040304

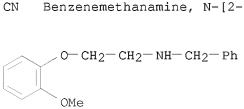
OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

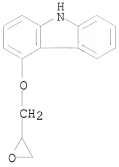
AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine
51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1, (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2, (R)-4-(Oxiranylmethoxy)-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

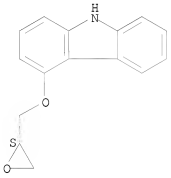


RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



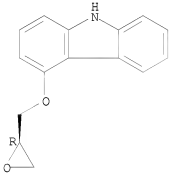
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 2004127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

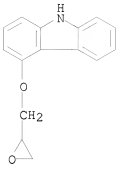
PRIORITY APPLN. INFO.:
EP 2001-101584 A 20010125
US 2002-54462 A3 20020122
WO 2002-EP583 W 20020122

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

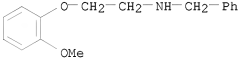
AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.

IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

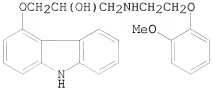


IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:270010 HCAPLUS
DOCUMENT NUMBER: 120:270010
TITLE: Synthesis of the enantiomers and three racemic metabolites of Carvedilol labeled to high specific activity with tritium
AUTHOR(S): Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.; Garnes, K. T.; Heys, J. R.
CORPORATE SOURCE: Dep. Synth. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1993), 33(12), 1091-105
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



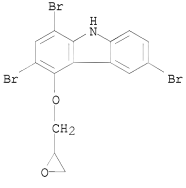
I

AB Carvedilol (SK&F 105517) (I) possesses unique cardiovascular activity, and is under development for indications such as angina and hypertension. Tritium labeled enantiomers of Carvedilol and racemates of three metabolites were needed for pharmacol. and drug metabolic studies. These compds. were synthesized by catalytic tritium-halogen exchange using tritium gas and 10% palladium-on-carbon catalyst. The precursors were polyhalogenated in the carbazole ring. Direct electrophilic bromination of the enantiomers of Carvedilol gave precursors that were converted to the corresponding tritiated final products by catalytic tritium halogen exchange. Bromination of 4-(2,3-epoxypropyloxy)-9H-carbazole gave an intermediate that was converted to the halogenated precursors of the racemic metabolites. Elaboration of this intermediate, 1,3,6-tribromo-4-(2,3-epoxypropyloxy)-9H-carbazole, to the desired metabolite precursors was achieved by nucleophilic epoxide opening with suitably functionalized N-benzyl aryloxyethylamines. Catalytic tritium-halogen exchange upon the brominated metabolite precursors was accompanied by cleavage of N- and O-benzyl protecting groups. Radiochem. purities of all tritiated final products were greater than 98% after preparative HPLC. Specific activities of the final products, determined by mass spectrometry, ranged from 35 to 76 Ci/mmol. Optical purity of the Carvedilol enantiomers, determined by chiral HPLC, was greater than 99%.

IT 154582-49-7P 154582-52-2P 154582-53-3P
154582-56-6P 154582-57-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate in preparation of tritium labeled Carvedilol)

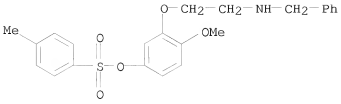
RN 154582-49-7 HCAPLUS

CN 9H-Carbazole, 1,3,6-tribromo-4-(oxiranylmethoxy)- (9CI) (CA INDEX NAME)

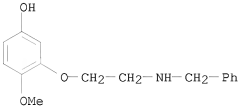


RN 154582-52-2 HCAPLUS

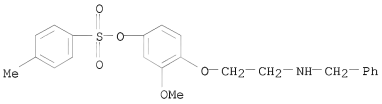
CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)



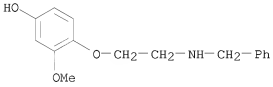
RN 154582-53-3 HCAPLUS
CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)



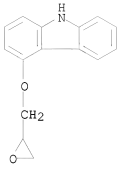
RN 154582-56-6 HCAPLUS
CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)



RN 154582-57-7 HCAPLUS
CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)



IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant, in preparation of tritium labeled Carvedilol)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



=> d l15 ibib abs hitstr tot

L15 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019

PRIORITY APPLN. INFO.: IN 2003-MU647 A 20030620
IN 2003-MU721 A 20030717
WO 2004-IN52 W 20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

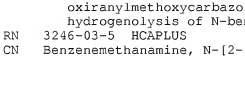
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine
51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1,
(S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2,
(R)-4-(Oxiranylmethoxy)-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

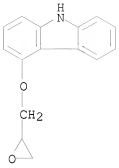
RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



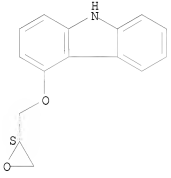
RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



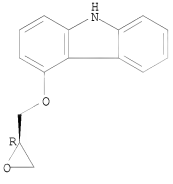
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 ibib abs hitstr tot

L17 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:38855 HCAPLUS
DOCUMENT NUMBER: 146:142505
TITLE: Process for preparation of carvedilol
INVENTOR(S): Kumar, Ashok; Saxena, Ashvini; Bhattacharyya, Anindya; Singh Sengar, Amit Vikram; Pathak, Gunjan Pramod; Soudagar, Satish Rajanikant; Mathur, Pramil Kumar; Nijasure, Avinash Manohar; Salunke, Sanjukumar Motiram; Gautam, Prashant; Ramsingh, Thakur Gajendrasingh; Jadhav, Dilip Uttam
PATENT ASSIGNEE(S): IPCA Laboratories Ltd., India
SOURCE: Eur. Pat. Appl., 11pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1741700	A1	20070110	EP 2006-116752	20060706
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
IN 2005MU00807	A	20070629	IN 2005-MU807	20050706
US 2007027202	A1	20070201	US 2006-480526	20060705
PRIORITY APPLN. INFO.:			IN 2005-MU807 A	20050706
OTHER SOURCE(S):	CASREACT 146:142505			

AB Disclosed herein is a process for preparation of carvedilol free from impurity, which comprises reaction of 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine in a polar aprotic solvent, followed by isolation of carvedilol as an acid addition salt and subsequent conversion into pure carvedilol.

IT 918903-19-2P 918903-21-6P 918903-23-8P
918903-28-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of carvedilol)

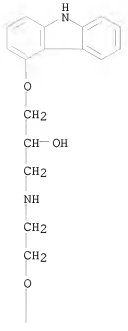
RN 918903-19-2 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, 4-methylbenzenesulfonate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

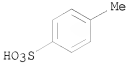
PAGE 1-A



PAGE 2-A

CM 2

CRN 104-15-4
CMF C7 H8 O3 S

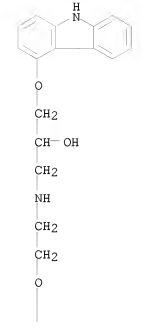


RN 918903-21-6 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, sulfate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



PAGE 2-A

CM 2

CRN 7664-93-9
CMF H2 O4 S

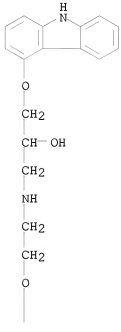
RN 918903-23-8 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, acetate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



PAGE 2-A

CM 2

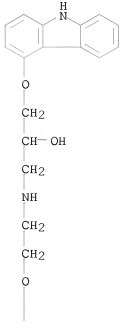
CRN 64-19-7
CMF C2 H4 O2

RN 918903-28-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, phosphate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



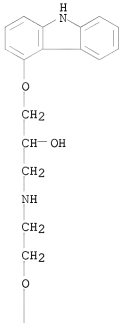
PAGE 2-A

CM 2

CRN 7664-38-2
CMF H3 O4 P

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol)
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

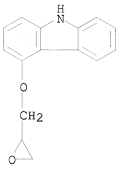
PAGE 1-A



PAGE 2-A

IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carvedilol)

RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:5582/8 HCAPLUS
DOCUMENT NUMBER: 145:62782
TITLE: Process for the preparation of carvedilol or its enantiomers from the ring-opening reaction of 4-(2,3-epoxypropoxy)carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy)ethylamine in ethyl acetate as the reaction solvent
INVENTOR(S): Trepat Guixer, Elisenda; Munoz Alvarez, Anna; Pomares Marco, Marta; Marquillas Olondriz, Francisco
PATENT ASSIGNEE(S): Zambon Group S.p.A., Italy
SOURCE: PCT Int. Appl., 11 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006061364	A1	20060615	WO 2005-EP56469	20051205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2589699	A1	20060615	CA 2005-2589699	20051205
EP 1838670	A1	20071003	EP 2005-815876	20051205
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,				

IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU

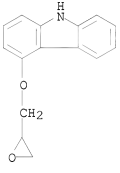
CN 101072753	A	20071114	CN 2005-80042214		20051205
IN 2007CN02478	A	20070907	IN 2007-CN2478		20070611
PRIORITY APPLN. INFO.:			EP 2004-106438	A	20041209
			WO 2005-EP56469	W	20051205

OTHER SOURCE(S): CASREACT 145:62782

AB A process for the preparation of carvedilol, as well as its optically active R and S enantiomers, comprises the ring-opening reaction of 4-(2,3-epoxypropoxy)carbazole, or its enantiomers, with an excess of 2-(2-methoxyphenoxy)ethylamine using Et acetate as the reaction solvent.

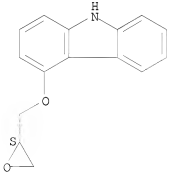
IT 51997-51-4, 4-(2,3-Epoxypropoxy)carbazole 95093-95-1
95093-96-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of carvedilol or its enantiomers from the ring-opening reaction of 4-(2,3-epoxypropoxy)carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy)ethylamine in Et acetate as the reaction solvent)

RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



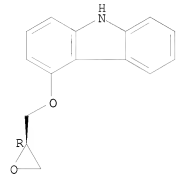
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



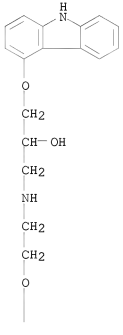
RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



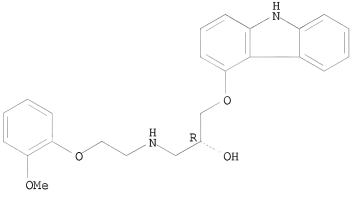
IT 72956-09-3P, Carvedilol 95093-99-5P, (R)-Carvedilol
95094-00-1P, (S)-Carvedilol
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of carvedilol or its enantiomers from the ring-opening reaction of 4-(2,3-epoxypropoxy)carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy)ethylamine in Et acetate as the reaction solvent)
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-
(CA INDEX NAME)

PAGE 1-A



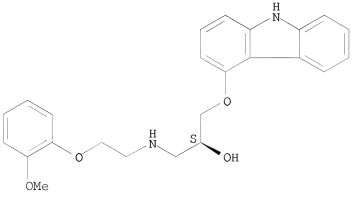
RN 95093-99-5 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



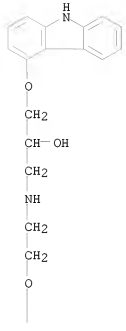
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1335682 HCAPLUS
DOCUMENT NUMBER: 146:274158
TITLE: A modified process to obtain Carvedilol
AUTHOR(S): Anon.
CORPORATE SOURCE: Spain
SOURCE: IP.com Journal (2005), 5(11A), 34 (No. IPCOM000130550D), 26 Oct 2005
CODEN: IJPOBX; ISSN: 1533-0001
PUBLISHER: IP.com, Inc.
DOCUMENT TYPE: Journal; Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IP 130550D		20051026		
PRIORITY APPLN. INFO.:			IP 2005-130550D	20051026

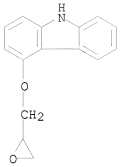
OTHER SOURCE(S): CASREACT 146:274158
AB Carvedilol [i.e., 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol], a β-adrenergic blocker, is obtained by the reaction of 4-[(2-oxiranyl)methoxy]-9H-carbazole with 2-(2-methoxyphenoxy)ethylamine hydrochloride in the presence of potassium carbonate in toluene solvent. In this process the byproduct [i.e., a dimer, 1,1'-[[2-(2-methoxyphenoxy)ethyl]imino]bis[3-(9H-carbazol-4-yloxy)-2-propanol]] is reduced to less than one percent. Carvedilol thus prepared meets EP specifications with only one crystallization
IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparation of carvedilol (minimizing byproduct formation) using [(oxiranyl)methoxy]carbazole with (methoxyphenoxy)ethylamine hydrochloride as starting materials, potassium carbonate as reagent and toluene as solvent)
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 51997-51-4, 4-Oxiranylmethoxy-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparation of carvedilol (minimizing byproduct formation) using [(oxiranyl)methoxy]carbazole with (methoxyphenoxy)ethylamine hydrochloride as starting materials, potassium carbonate as reagent and toluene as solvent)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

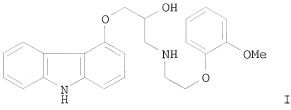


L17 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1288806 HCAPLUS
DOCUMENT NUMBER: 144:22811
TITLE: A novel process for the preparation of 1-(9H-carbazol-4-yloxy)-3-[[2-(-methoxyphenoxy)-ethyl] amino]-propan-2-ol (carvedilol)
INVENTOR(S): Tarur, Venkatasubramanian Radhakrishnan; Sathe, Dhananjay Govind; Kulkarni, Swapnil Jayant
PATENT ASSIGNEE(S): USV Limited, India
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005115981	A2	20051208	WO 2005-IN139	20050503
WO 2005115981	A3	20060119		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2004MU00479	A	20060616	IN 2004-MU479	20040422
US 2007191456	A1	20070816	US 2006-568732	20061227

PRIORITY APPLN. INFO.: IN 2004-MU479 A 20040422
WO 2005-IN139 W 20050503

OTHER SOURCE(S): CASREACT 144:22811
GI



I

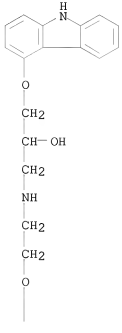
AB This invention disclosed a novel process for preparation of carvedilol (I) in high purity by using eco friendly solvents. The process comprised reacting 4-hydroxycarbazole with epichlorhydrin in presence of an organic solvent and a base at temps. between 10° and 30°, and then reacting the resultant 4-(2,3-epoxypropoxy)carbazole with a salt of 2-(2-methoxyphenoxy)ethylamine, preferably the hydrochloride salt, in presence of a base and a hydroxylic solvent at temps. between 30° and 90°.

IT 72956-09-3P, 1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(eco friendly process for the preparation of carvedilol, a pharmaceutically useful adrenergic β-receptor antagonist)

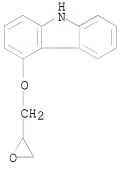
RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



IT 51997-51-4P, 4-(2,3-Epoxypropoxy)carbazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(eco friendly process for the preparation of carvedilol, a pharmaceutically useful adrenergic β-receptor antagonist)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L17 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1260624 HCAPLUS
DOCUMENT NUMBER: 144:22806
TITLE: Process for the preparation of carvedilol
INVENTOR(S): Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Limited, India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005113502	A1	20051201	WO 2005-GB1978	20050519

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,

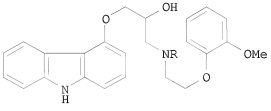
SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2005245182	A1	20051201	AU 2005-245182		20050519
CA 2566197	A1	20051201	CA 2005-2566197		20050519
EP 1756057	A1	20070228	EP 2005-744187		20050519
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
JP 2007538061	T	20071227	JP 2007-517424		20050519
IN 2006MN01302	A	20070608	IN 2006-MN1302		20061107
PRIORITY APPLN. INFO.:			GB 2004-11273	A	20040520
			WO 2005-GB1978	W	20050519

OTHER SOURCE(S): CASREACT 144:22806

GI



I

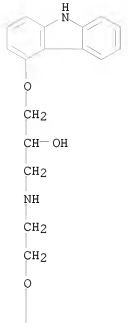
AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H4O(CH2)2NHCH2Ph using K2CO3 in water to give carvedilol N-benzyl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pd/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic β-receptor antagonists, vasodilators and treatment of angina pectoris.

IT 72956-09-3P, Carvedilol
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 72956-09-3 HCAPLUS

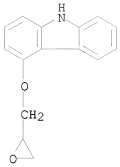
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1128799 HCAPLUS
DOCUMENT NUMBER: 143:386916
TITLE: An improved process for the manufacture of carvedilol
INVENTOR(S): Kankan, Rajendra Narayan Rao; Rao, Dharamraj Ramchandra
PATENT ASSIGNEE(S): Cipla Ltd., India
SOURCE: Indian, 11 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 186587	A1	20011006	IN 1999-BO583	19990817
PRIORITY APPLN. INFO.:			IN 1999-BO583	19990817

OTHER SOURCE(S): CASREACT 143:386916; MARPAT 143:386916
GI

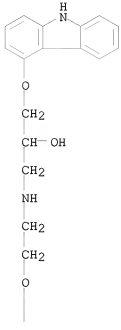
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An improved process for the manufacture of Carvedilol I, a potent antihypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [R1 = (un)substituted CH2Ph; formed by reacting carbazole III with a substituted amine IV]. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl]benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [R1 = Ch2Ph] afforded carvedilol I.

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(improved process for the manufacture of carvedilol)

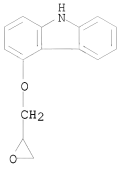
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-
(CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 51997-51-4, 4-(2,3-Epoxypropoxy)carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(improved process for the manufacture of carvedilol)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L17 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:962205 HCAPLUS
DOCUMENT NUMBER: 143:266815
TITLE: Process for the manufacture of racemic carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine
INVENTOR(S): Shah, Dhiraj R.; Naik, Ashish P.; Purohit, Parva Y.; Sharma, Rajivkumar; Agarwal, Virendra Kumar
PATENT ASSIGNEE(S): Cadila Healthcare Limited, India
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005080329	A2	20050901	WO 2005-IN56	20050222
WO 2005080329	A3	20060928		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2004MU00219	A	20060120	IN 2004-MU219	20040223
CA 2560353	A1	20050901	CA 2005-2560353	20050222
EP 1723107	A2	20061122	EP 2005-747343	20050222
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
PRIORITY APPLN. INFO.:			IN 2004-MU219	A 20040223
			WO 2005-IN56	W 20050222

OTHER SOURCE(S): CASREACT 143:266815; MARPAT 143:266815
AB Carvedilol of high HPLC purity (>99.5 %) is prepared by the ring-opening

addition reaction of 4-(oxiran-2-ylmethoxy)-9H-carbazole with 2-(2-methoxyphenoxy)ethylamine followed by salification of the impure carvedilol with an organic acid (e.g., salicylic acid) and neutralization of the carvedilol salt (e.g., carvedilol salicylate) with a base to give pure carvedilol.

IT 787598-89-4P, Carvedilol oxalate 787598-91-8P, Carvedilol salicylate 863664-91-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in a process for the manufacture of racemic carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine)

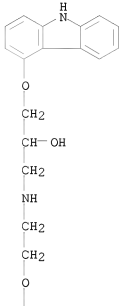
RN 787598-89-4 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



PAGE 2-A

CM 2

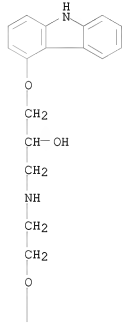
CRN 144-62-7
CMF C2 H2 O4

RN 787598-91-8 HCAPLUS
CN Benzoic acid, 2-hydroxy-, compd. with 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (1:1) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



PAGE 2-A

CM 2

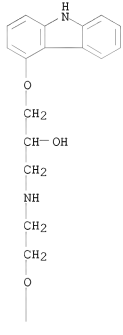
CRN 69-72-7
CMF C7 H6 O3

RN 863664-91-9 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A

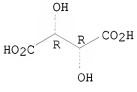


PAGE 2-A

CM 2

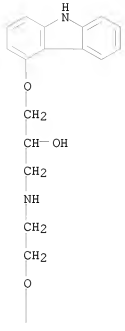
CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



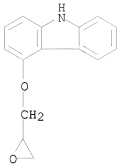
IT 72956-09-3P, Carvedilol
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the manufacture of racemic carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine)
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the manufacture of racemic carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L17 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647 A	20030620
			IN 2003-MU721 A	20030717
			WO 2004-IN52 W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

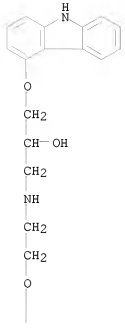
AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 72956-09-3P, Carvedilol 95093-99-5P, (R)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol 95094-00-1P, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

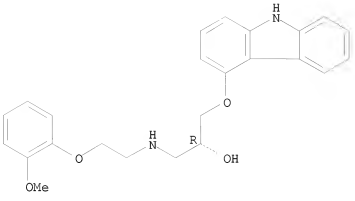
PAGE 1-A



PAGE 2-A

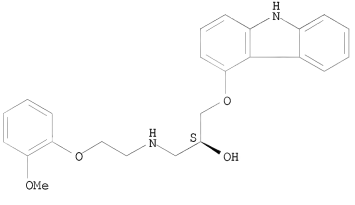
RN 95093-99-5 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

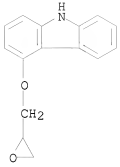


RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

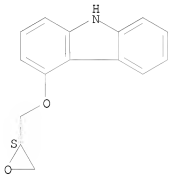


IT 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1, (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2, (R)-4-(Oxiranylmethoxy)-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



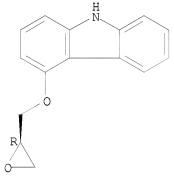
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:927171 HCAPLUS
DOCUMENT NUMBER: 141:395415
TITLE: Process for the preparation of crystalline carvedilol form-II
INVENTOR(S): Ramanjaneyulu, Gorantla Seeta; Kumar, Indukuri Venkata Sunil; Rao, Ketavarapu Narasimha; Kishore, Jammula Vera Venkata Krishna
PATENT ASSIGNEE(S): Matrix Laboratories Ltd., India
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004094378	A1	20041104	WO 2004-IN104	20040416
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MA00328	A	20070518	IN 2003-MA328	20030421
EP 1615888	A1	20060118	EP 2004-727971	20040416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
US 2007055069	A1	20070308	US 2005-552843	20051012
PRIORITY APPLN. INFO.:			IN 2003-MA328 A	20030421
			WO 2004-IN104 W	20040416

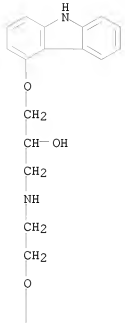
OTHER SOURCE(S): CASREACT 141:395415

AB The present invention provides a cost-effective, industrially feasible process for the manufacture of crystalline carvedilol form-II using novel carvedilol salts comprising a step of reacting 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine followed by acidification with mineral acid in presence of an organic solvent to yield acid addition salts, (e.g. carvedilol oxalate), treatment of the said salts with base(s) in presence of organic solvent(s), water, and isolation from the organic solvent(s) followed by crystallization from Et acetate.

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation of crystalline carvedilol form-II by reaction of 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine)

RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A

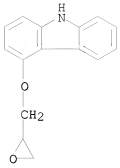


PAGE 2-A

IT 51997-51-4P, 4-(2,3-Epoxypropoxy)carbazole 787598-89-4P, Carvedilol oxalate 787598-91-8P, Carvedilol salicylate
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of crystalline carvedilol form-II by reaction of 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

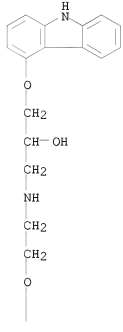


RN 787598-89-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



PAGE 2-A

CM 2

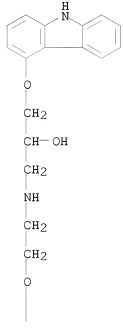
CRN 144-62-7
CMF C2 H2 O4

RN 787598-91-8 HCAPLUS
CN Benzoic acid, 2-hydroxy-, compd. with 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (1:1) (CA INDEX NAME)

CM 1

CRN 72956-09-3
CMF C24 H26 N2 O4

PAGE 1-A



CM 2

CRN 69-72-7
CMF C7 H6 O3

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:412919 HCAPLUS
DOCUMENT NUMBER: 140:406735
TITLE: Process for the preparation of carvedilol from 4-(oxirane-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine salts
INVENTOR(S): Hercek, Richard; Skoda, Alojz; Proksa, Bohumil
PATENT ASSIGNEE(S): Zentiva, A.S., Slovakia
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004041783	A1	20040521	WO 2003-SK20	20031104
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
SK 285547	B6	20070301	SK 2002-1595	20021108
AU 2003301861	A1	20040607	AU 2003-301861	20031104

EP 1558575 A1 20050803 EP 2003-810732 20031104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
US 2006167077 A1 20060727 US 2005-533809 20050505
PRIORITY APPLN. INFO.: SK 2002-1595 A 20021108
WO 2003-SK20 W 20031104
OTHER SOURCE(S): CASREACT 140:406735

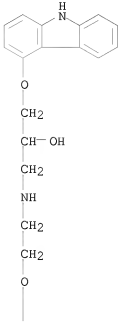
AB Carvedilol is prepared in high yield and selectivity by the reaction of 4-(oxirane-2-ylmethoxy)-9H-carbazole with acid-addition salts of 2-(2-methoxyphenoxy)ethylamine [e.g., 2-(2-methoxyphenoxy)ethylamine hydrochloride] in the presence of a base (e.g., potassium carbonate) in an C2-5 alc. solvent (e.g., isopropanol) at an elevated temperature (e.g., 83°).

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation of carvedilol from 4-(oxirane-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine salts)

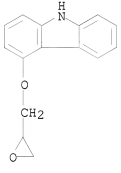
RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of carvedilol from 4-(oxirane-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine salts)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L17 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002247645	A1	20020806	AU 2002-247645		20020122
EP 1355880	A2	20031029	EP 2002-716673		20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004519465	T	20040702	JP 2002-559391		20020122
IN 2003CN01126	A	20050422	IN 2003-CN1126		20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606		20030723
US 2004127723	A1	20040701	US 2004-763296		20040122
US 7169935	B2	20070130			
PRIORITY APPLN. INFO.:			EP 2001-101584	A	20010125
			US 2002-54462	A3	20020122
			WO 2002-EP583	W	20020122

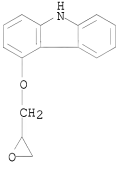
OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.

IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 51997-51-4 HCAPLUS

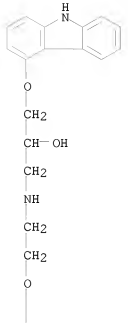
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:10275 HCAPLUS
DOCUMENT NUMBER: 136:90914
TITLE: Preparation of carvedilol and its crystalline hydrate and solvate
INVENTOR(S): Hildesheim, Jean; Finogueev, Sergey; Aronhime, Judith; Dolitzky, Ben-Zion; Ben-Valid, Shoshana; Kor, Ilan
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000216	A1	20020103	WO 2001-US20760	20010628
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2413702	A1	20020103	CA 2001-2413702	20010628
US 2002143045	A1	20021003	US 2001-894798	20010628
US 6699997	B2	20040302		
EP 1299101	A1	20030409	EP 2001-950671	20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2003001802	A2	20030929	HU 2003-1802	20010628
JP 2004501191	T	20040115	JP 2002-504998	20010628
CN 1733727	A	20060215	CN 2005-10086095	20010628
EP 1655285	A1	20060510	EP 2005-21195	20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
ZA 2002010282	A	20031219	ZA 2002-10282	20021219
MX 2002PA12795	A	20040730	MX 2002-PA12795	20021219
US 2004152757	A1	20040805	US 2004-758025	20040116
US 7056942	B2	20060606		
US 2004225132	A1	20041111	US 2004-758026	20040116
US 7126008	B2	20061024		
US 2006030614	A1	20060209	US 2005-217643	20050831
AU 2007200344	A1	20070215	AU 2007-200344	20070125

PRIORITY APPLN. INFO.:		
US 2000-214356P	P	20000628
US 2000-246358P	P	20001107
AU 2001-271639	A3	20010628
CN 2001-814616	A3	20010628
EP 2001-950671	A3	20010628
US 2001-894798	A3	20010628
WO 2001-US20760	W	20010628
US 2004-758025	A3	20040116

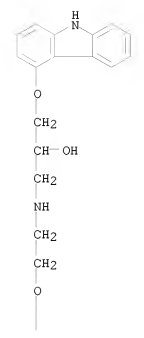
AB This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compns. thereof. Carvedilol was prepared by the reaction of 2-(2-methoxyphenoxy)ethylamine and 4-(oxiran-2-ylmethoxy)-9H-carbazole. Crystalline carvedilol form II was prepared by crystallizing carvedilol from isoamyl alc.

IT 72956-09-3P, Carvedilol 385765-36-6P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of carvedilol and its crystalline hydrate and solvate)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

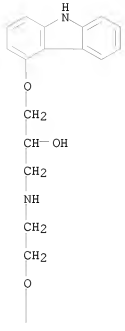
PAGE 1-A



PAGE 2-A

RN 385765-36-6 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, hydrochloride, hydrate (9CI) (CA INDEX NAME)

PAGE 1-A

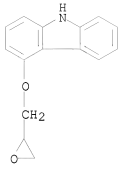


PAGE 2-A

● x HCl

● x H_2O

IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carvedilol and its crystalline hydrate and solvate)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747161 HCAPLUS
DOCUMENT NUMBER: 135:288689
TITLE: Process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-ol [carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:

HU 1997-2209	A	19971124
HU 1998-2180	A	19981001
EP 1998-122114	A3	19981124
RU 1998-120700	A	19981118

OTHER SOURCE(S): CASREACT 135:288689
AB A process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-

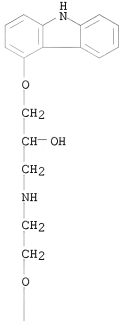
methoxyphenoxy)ethyl}amino]propan-2-ol as well as acid addition salts of this compound, was developed in which the N-[2-(2'-methoxy-phenoxy)-ethyl]benzylamine is reacted with epichlorohydrin, and the formed 1-N-benzyl-2'-[{(2'-methoxy-phenoxy)ethyl}amino]-3-propan-2-ol is reacted with 4-hydroxy-9H-carbazole and the resulting 1-N-benzyl-2'-(methoxyphenoxyethylamino)-3-[9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol thus obtained is reacted with acids to yield acid addition their salts, or if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2}-(2'-methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts thereof and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-{2}-(2'-methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, separating the enantiomers.

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

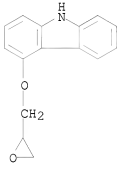
RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A



IT 51997-51-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



L17 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:344783 HCAPLUS
DOCUMENT NUMBER: 130:352184
TITLE: Preparation of carvedilol
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001

CZ 296521	B6	20060412	CZ 1998-3561		19981104
CZ 297445	B6	20061213	CZ 2004-1111		19981104
HR 980590	B1	20031231	HR 1998-590		19981112
SK 284109	B6	20040908	SK 1998-1560		19981112
RU 2216539	C2	20031120	RU 1998-120700		19981118
RU 2245875	C2	20050210	RU 2003-107772		19981118
EP 1142873	A2	20011010	EP 2001-111213		19981124
EP 1142873	A3	20030910			
EP 1142873	B1	20040421			
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO					
EP 1142874	A2	20011010	EP 2001-111214		19981124
EP 1142874	A3	20031022			
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO					
ES 2196459	T3	20031216	ES 1998-122114		19981124
ES 2221875	T3	20050116	ES 2001-111213		19981124
PRIORITY APPLN. INFO.:			HU 1997-2209	A	19971124
			HU 1998-2180	A	19981001
			RU 1998-120700	A	19981118
			EP 1998-122114	A3	19981124

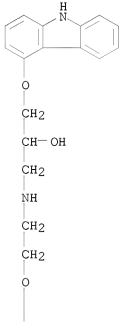
AB The title process comprises, e.g., condensation of 4-oxiranylmethoxy-9H-carbazole with 2-(MeO)C6H4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.

IT 72956-09-3P, Carvedilol 95093-99-5P, (+)-Carvedilol 95094-00-1P, (-)-Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol)

RN 72956-09-3 HCAPLUS

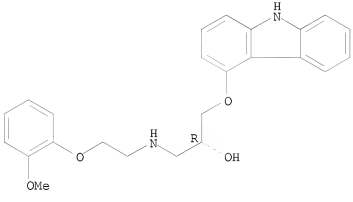
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



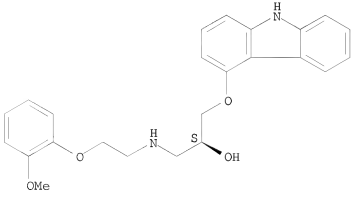
RN 95093-99-5 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



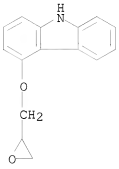
RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



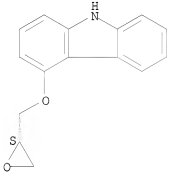
IT 51997-51-4, 4-Oxiranylmethoxy-9H-carbazole 95093-95-1,

(S)-4-Oxiranylmethoxy-9H-carbazole 95093-96-2,
(R)-4-Oxiranylmethoxy-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carvedilol)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



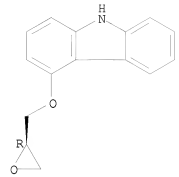
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

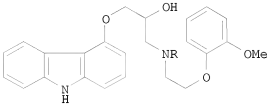
=> d l18 ibib abs hitstr tot

L18 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1260624 HCAPLUS
DOCUMENT NUMBER: 144:22806
TITLE: Process for the preparation of carvedilol
INVENTOR(S): Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Limited, India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005113502	A1	20051201	WO 2005-GB1978	20050519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005245182	A1	20051201	AU 2005-245182	20050519
CA 2566197	A1	20051201	CA 2005-2566197	20050519
EP 1756057	A1	20070228	EP 2005-744187	20050519
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2007538061	T	20071227	JP 2007-517424	20050519
IN 2006MN01302	A	20070608	IN 2006-MN1302	20061107

PRIORITY APPLN. INFO.: GB 2004-11273 A 20040520
WO 2005-GB1978 W 20050519
OTHER SOURCE(S): CASREACT 144:22806

GI



I

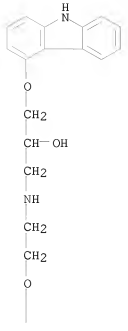
AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H4O(CH2)2NHCH2Ph using K2CO3 in water to give carvedilol N-benzyl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pd/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic β-receptor antagonists, vasodilators and treatment of angina pectoris.

IT 72956-09-3P, Carvedilol
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 72956-09-3 HCAPLUS

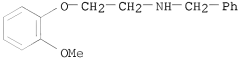
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1128799 HCAPLUS
DOCUMENT NUMBER: 143:386916
TITLE: An improved process for the manufacture of carvedilol
INVENTOR(S): Kankan, Rajendra Narayan Rao; Rao, Dharamraj Ramchandra
PATENT ASSIGNEE(S): Cipla Ltd., India
SOURCE: Indian, 11 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 186587	A1	20011006	IN 1999-BO583	19990817

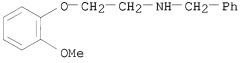
PRIORITY APPLN. INFO.: IN 1999-BO583 19990817
OTHER SOURCE(S): CASREACT 143:386916; MARPAT 143:386916
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An improved process for the manufacture of Carvedilol I, a potent antihypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [R1 = (un)substituted CH2Ph; formed by reacting carbazole III with a substituted amine IV]. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl]benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [R1 = Ch2Ph] afforded carvedilol I.

IT 120606-08-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(improved process for the manufacture of carvedilol)

RN 120606-08-8 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

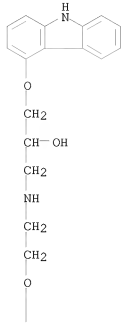


● HCl

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(improved process for the manufacture of carvedilol)

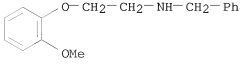
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-
(CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(improved process for the manufacture of carvedilol)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



L18 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019

PRIORITY APPLN. INFO.:
IN 2003-MU647 A 20030620
IN 2003-MU721 A 20030717
WO 2004-IN52 W 20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for

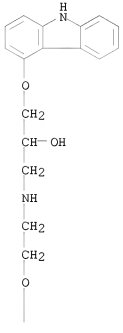
checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 72956-09-3P, Carvedilol 95093-99-5P, (R)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol 95094-00-1P, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72956-09-3 HCAPLUS

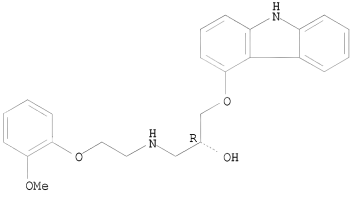
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



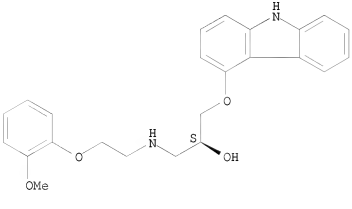
RN 95093-99-5 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and

hydrogenolysis of N-benzylcarvedilol)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

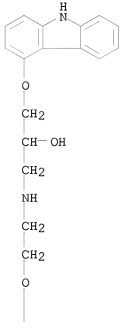
L18 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 2004127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

PRIORITY APPLN. INFO.:		
EP 2001-101584	A	20010125
US 2002-54462	A3	20020122
WO 2002-EP583	W	20020122

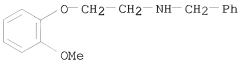
OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080
AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.
IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)
RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747161 HCAPLUS
DOCUMENT NUMBER: 135:288689
TITLE: Process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-ol [carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:
HU 1997-2209 A 19971124
HU 1998-2180 A 19981001
EP 1998-122114 A3 19981124
RU 1998-120700 A 19981118

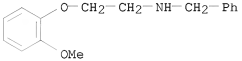
OTHER SOURCE(S): CASREACT 135:288689

AB A process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol as well as acid addition salts of this compound, was developed in which the N-[2-(2'-methoxy-phenoxy)-ethyl]benzylamine is reacted with epichlorohydrin, and the formed 1-N-benzyl-2'-[{(2'-methoxy-phenoxy)ethyl}amino]-3-propan-2-ol is reacted with 4-hydroxy-9H-carbazole and the resulting 1-N-benzyl-2'-(methoxyphenoxyethylamino)-3-[9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the

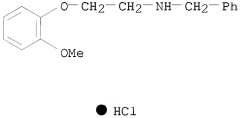
1-[9'H-carbazol-4'-yloxy]-3-[[2'-(2'-methoxyphenoxy)ethyl]amino]propan-2-ol thus obtained is reacted with acids to yield acid addition their salts, or if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2}-(2'-methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts thereof and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-{2}-(2'-methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, separating the enantiomers.

IT 3246-03-5P 120606-08-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



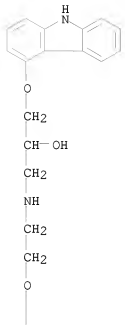
RN 120606-08-8 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)



IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L18 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:344783 HCAPLUS
DOCUMENT NUMBER: 130:352184
TITLE: Preparation of carvedilol
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
CZ 296521	B6	20060412	CZ 1998-3561	19981104
CZ 297445	B6	20061213	CZ 2004-1111	19981104
HR 980590	B1	20031231	HR 1998-590	19981112
SK 284109	B6	20040908	SK 1998-1560	19981112
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
ES 2196459	T3	20031216	ES 1998-122114	19981124
ES 2221875	T3	20050116	ES 2001-111213	19981124

PRIORITY APPLN. INFO.:

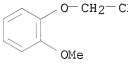
HU 1997-2209	A	19971124
HU 1998-2180	A	19981001
RU 1998-120700	A	19981118
EP 1998-122114	A3	19981124

AB The title process comprises, e.g., condensation of 4-oxiranylmethoxy-9H-carbazole with 2-(MeO)C6H4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.

IT 3246-03-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol)

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

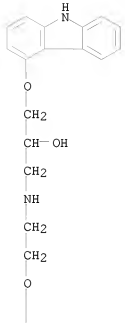


IT 72956-09-3P, Carvedilol 95093-99-5P, (+)-Carvedilol 95094-00-1P, (-)-Carvedilol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

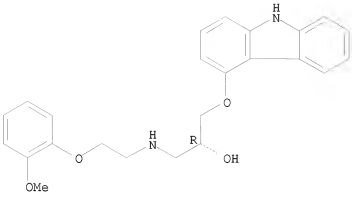
PAGE 1-A



PAGE 2-A

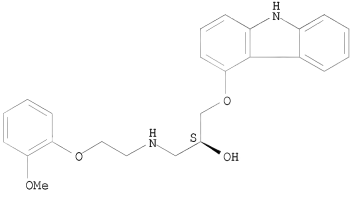
RN 95093-99-5 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l19 ibib abs hitstr tot

L19 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647 A	20030620
			IN 2003-MU721 A	20030717
			WO 2004-IN52 W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and

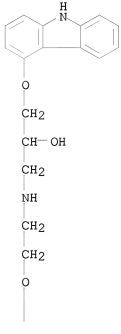
toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 72956-09-3P, Carvedilol 95093-99-5P, (R)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol 95094-00-1P, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A

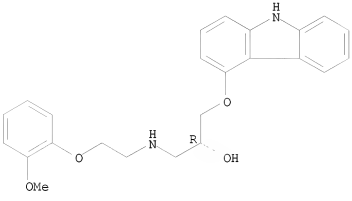


PAGE 2-A

RN 95093-99-5 HCAPLUS

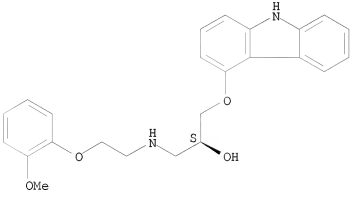
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

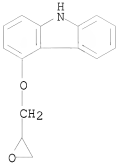


RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

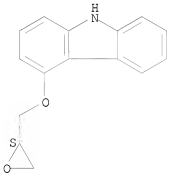


IT 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1, (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2, (R)-4-(Oxiranylmethoxy)-9H-carbazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



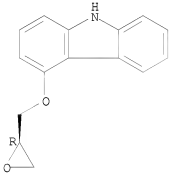
RN 95093-95-1 HCAPLUS
CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 95093-96-2 HCAPLUS
CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 2004127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

PRIORITY APPLN. INFO.:

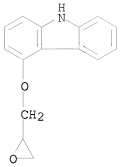
EP 2001-101584	A	20010125
US 2002-54462	A3	20020122
WO 2002-EP583	W	20020122

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.

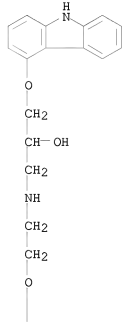
IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 51997-51-4 HCAPLUS
CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)



RN 72956-09-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-
(CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L20 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 2006270858	A1	20061130	US 2005-553957	20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647 A	20030620
			IN 2003-MU721 A	20030717
			WO 2004-IN52 W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R

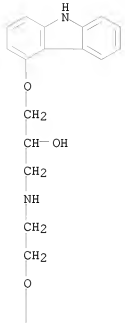
or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 72956-09-3P, Carvedilol 95093-99-5P, (R)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol 95094-00-1P, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

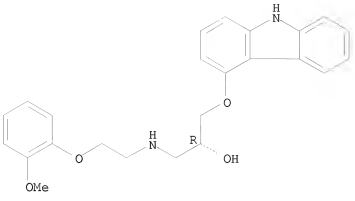
PAGE 1-A



PAGE 2-A

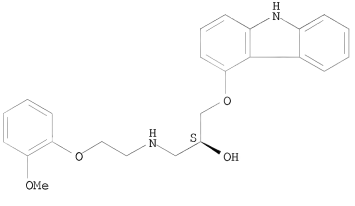
RN 95093-99-5 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

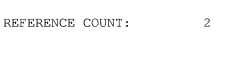


RN 95094-00-1 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 2004127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

PRIORITY APPLN. INFO.:		EP 2001-101584	A 20010125
		US 2002-54462	A3 20020122
		WO 2002-EP583	W 20020122

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

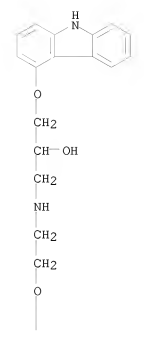
AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.

IT 72956-09-3P, Carvedilol
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 72956-09-3 HCAPLUS

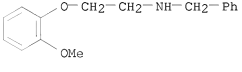
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)
RN 3246-03-5 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> log y
COST IN U.S. DOLLARS SINCE FILE TOTAL

	ENTRY	SESSION
FULL ESTIMATED COST	231.24	786.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-29.60	-29.60

STN INTERNATIONAL LOGOFF AT 14:11:02 ON 07 JAN 2008